Fifty cases of late prosthetic valve endocarditis: improvement in prognosis over a 15 year period

C LEPORT,* J L VILDE,* F BRICAIRE,* A COHEN,* B PANGON,†
C GAUDEBOUT,‡ P E VALERE§

From the *Service des Maladies Infectieuses et Tropicales, †Laboratoire de Microbiologie, ‡INSERM U13
Hôpital Claude Bernard; and §Service de Cardiologie, Hôpital Beaujon, Paris, France

SUMMARY The clinical course, prognostic factors, and management of 50 cases of late prosthetic valve endocarditis, occurring more than two months after valve replacement, were reviewed. Twenty nine cases that presented from 1971 to 1980 were compared with 21 cases that presented from 1981 to 1985. Apart from an appreciable decrease in the frequency of neurological complications between the first period (38%) and the second period (10%) no differences in clinical or bacteriological features were seen. Seventeen (59%) of the 29 cases in the earlier period and four (19%) of the 21 cases in the later period died. The rationale for antimicrobial treatment was similar during both periods. Cardiac surgery was performed in eight of 29 cases between 1971 and 1980 and in 11 of 21 between 1981 and 1985; the mean (SD) time between diagnosis of endocarditis and operation was 28 (19) days and 43 (44) days respectively. Six of the eight cases operated on in the first period died as did two of the 11 operated on in the second period. Twenty seven of the 29 cases presenting between 1971 and 1980 were treated with anticoagulants—either warfarin (15 of 27) or heparin sodium (12 of 27). Sixteen of the 21 cases presenting later were given anticoagulants and 15 of these cases were given heparin sodium. Control of anticoagulation was inadequate in nine of the 27 cases treated with anticoagulants during the first period and in only two of 16 treated during the second period. During the first treatment period neurological complications were more frequent when control of anticoagulation was inadequate.

Since the first reports of prosthetic valve endocarditis in 1962–63[1] the number of cases has increased. This is the result of an increase in the number of patients undergoing valve replacement and of the longer survival of these patients. The overall prevalence of late prosthetic valve endocarditis, however, remains approximately 1·2%.[2]

In a review in 1979 of 140 cases of late prosthetic valve endocarditis Watanakunakorn reported a mean death rate of 45%.[3] The wide variation in mortality (from 18% to 67%) in various series indicates that many factors can influence prognosis.[4][5]

We have already reported our experience with 29 cases of late prosthetic valve endocarditis studied retrospectively from 1971 to 1980 at the Claude Bernard Hospital.[6] We have reviewed a further 21 cases

examined between 1981 and 1985 and we have compared them with the earlier series in an attempt to analyse the factors contributing to any changes in the pattern and prognosis of the disease.

Patients and methods

From January 1971 to December 1985 there were 50 cases of late prosthetic valve endocarditis among the 449 cases of infective endocarditis seen at the Department of Infectious and Tropical Diseases, Claude Bernard Hospital, Paris.

Late prosthetic valve endocarditis was defined as an infection occurring more than two months after valve replacement.[7] Diagnosis was based on the following criteria: (a) anatomical evidence of endocarditis (22/50 cases) and (b) at least two positive blood cultures containing the same organism and a consistent clinical picture (43 of 50 cases). In the seven cases with negative blood cultures the diagnosis was confirmed anatomically in five and was prob-
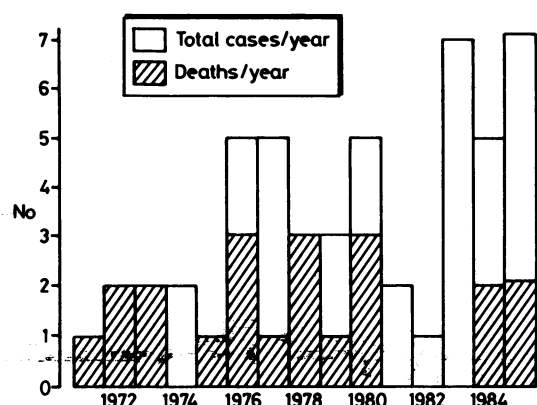
Figure *Number of cases and mortality of late prosthetic valve endocarditis, 1971–85.*

able in two. A relapse was defined as a subsequent episode of endocarditis in which the same organism as in the original episode was implicated and a recurrence as a subsequent episode in which an organism other than the original one was implicated.

The cases were divided into two groups (figure). Twenty nine cases occurred during the earlier period (between 1971 and 1980) in 26 patients (17 men and nine women; mean (SD) age 51 (14) years (range 20–70)). One patient had three recurrences. There were twenty one further cases during the later period (between 1981 and 1985) in 20 patients (13 men and seven women; mean (SD) age 46 (19) years, range 11–75) and one patient had a recurrence.

The two periods were compared by the χ^2 test (both with and without Yates' correction), the Fisher exact probability test, the Mann-Whitney U test, the analysis of variance, and Student's t test. A p value of $\leqslant 0.05$ was taken to indicate statistical significance.

Results

CLINICAL AND BACTERIOLOGICAL FEATURES
During the first period all 29 cases had mechanical valves, whereas during the second period eight of 21 had heterograft valves (p < 0.001). The sites of the prostheses were similar in the two periods (table 1).

The only significant difference in the clinical features of the disease between the two periods was the decrease in cerebral events, from 11 (38%) of 29 cases in 1971–80 to two (10%) of 21 cases in 1981–85 (p < 0.05) (table 2).

There was no significant difference in the bacteriological profile between the two groups (table 3). The frequency of non-streptococcal endocarditis (16/29 in 1971–80 and 11/21 in 1981–85) was similar during the two periods.

Table 1 *Comparison of the site of the prostheses in late prosthetic valve endocarditis between two groups treated over two periods*

	Number of cases	
	1971–80	*1981–85*
Aortic	9	12
Mitral	8	3
Tricuspid	0	3
Multiple	12	3
Total	29	21

Table 2 *Clinical features in cases of late prosthetic valve endocarditis during the two periods*

	Number of cases (%)	
	1971–80 (29 cases)	*1981–85 (21 cases)*
Fever	29 (100)	20 (95)
Splenomegaly	7 (24)	5 (24)
New heart murmur	13 (45)	11 (52)
Congestive heart failure	17 (59)	10 (48)
Cerebral event	11* (38)	2* (10)

*The only significant difference between the two periods was that for cerebral events (p < 0.05).

Table 3 *Bacteriological features of cases of late prosthetic valve endocarditis during the two periods*

	Number of cases (%)	
	1971–80	*1981–85*
Streptococcus:	13* (45)	10* (48)
Str enterococcus (group D)	7	4
Str bovis (group D)	3	1
Non-group D	3	5
Staphylococcus:	10 (34)	3 (14)
Staph aureus	6	2
Coagulase negative	4	0
micrococcus sp	0	1
Other micro-organism	2†	3‡
Two causative agents	3§	1¶
Negative blood and valve cultures	1	4**
Total	29	21

*Frequency of streptococcal endocarditis in the two periods (p = NS).
†*Klebsiella* in one case and *Pseudomonas* in the other.
‡*Corynebacterium* in one case, *Cardiobacterium hominis* in one, and *Histoplasma capsulatum* in one case.
§*Streptococcus faecalis* and *Pseudomonas stutzeri* in one case, *Staphylococcus* coagulase negative and *Candida tropicalis* in one case, and *Streptococcus faecalis* and *Enterobacter cloacae* in one case.
¶*Streptococcus sanguis* 1 and *Streptococcus sanguis* 2 in one case.
**Serological evidence of *Coxiella burnetii* endocarditis in one case.

OUTCOME
The overall mortality for the two periods was 42% (21 of 50 cases). Seventeen (59%) cases in the first group died and four (19%) in the second (p < 0.01). Death was related to cardiac failure in 10 of the 17 earlier cases and in two of the four later cases; a neurological complication accounted for the deaths of

seven of 17 cases from 1971 to 1980 and two of the four cases from 1981 to 1985.

The only relapse occurred in the more recent period in a patient who was treated with antimicrobials alone for endocarditis caused by *Streptococcus D faecium*. This patient was successfully treated with antimicrobials and valve replacement. Between 1971 and 1980 one patient died after three recurrences caused by *Streptococcus faecalis*, and finally *Streptococcus bovis* and *Pseudomonas aeruginosa*. Between 1981 and 1985 there was one recurrence caused by *Straphylococcus aureus* in a drug addict with a tricuspid prosthesis who had previously been infected with *Streptococcus sanguis*.

ANTIMICROBIAL TREATMENT
All but one of the 50 cases was treated with antibiotics; in the first period one patient died before treatment could be started. The choice of antimicrobial agents was based on the same principles during both periods; the agent was selected according to the causative organism, the in vitro susceptibility tests, and the serum bactericidal titre. A combined drug regimen was used in 45 of 47 cases of non-fungal endocarditis. The mean (SD) interval between the first manifestations of endocarditis and the onset of antimicrobial treatment was 23 (18) days (range 2–59) for 1971–80 and 25 (36) days (range 2–145) for 1981–85 (NS). The duration of treatment in non-fungal endocarditis was significantly longer in recent years—54 (32) days (range 3–146) versus 34 (20) days (range 2–80) (p < 0·01). In 1971–80, however, seven of 27 patients died before day 15 of treatment, whereas in 1981–85 only one of 20 patients did.

SURGICAL TREATMENT
Nineteen patients underwent valve replacement during the active phase of the disease (eight of the 29 initial cases and 11 of the 21 more recent cases). Analysis of prognostic factors from 1971 to 1980[6] led to more precise indications for operation being applied in recent years; these were based on criteria established by Karchmer *et al*.[8] Thus operation was more common during 1981–85; however, this difference was not statistically significant (p = 0·08). The mean (SD) interval between the diagnosis of endocarditis and the valve replacement was not significantly different during the two periods: 28 (19) days (range 2–60) in 1971–80 and 43 (44) days (range 8–150) in 1981–85. In the first period, six (75%) of eight surgically treated patients died and in the second period two (18%) of 11 died (p < 0·05). Culture of the prosthesis in 17 of 19 surgically treated cases was sterile in eight cases. In seven others it grew the same or one of the organism(s)

present in the blood cultures and in two cases it grew an organism which had not been isolated from the blood—*Histoplasma capsulatum* in one case and *Streptococcus mitis* in the other.

ANTICOAGULANT TREATMENT
Anticoagulant treatment was continued in 43 of 50 cases in which it had been used before the development of endocarditis. From 1971 to 1980, 27 of 29 cases were given anticoagulants—15 warfarin and 12 heparin sodium. During this period two patients treated with warfarin had neuromeningeal bleeding with a prothrombin time of less than 10%, without the dose of anticoagulant being changed. For this reason during the second period we treated 15 of 16 cases with heparin sodium rather than warfarin. Satisfactory coagulation tests (that is, activated partial thromboplastin time between 1·5 and 2·5 times control or prothrombin time between 20% and 40% control) were more often maintained during recent years, 14 of 16 cases, than in the past, 18 of 27 cases.

During the first period, neurological complications were more frequent when anticoagulation was inadequate (p < 0·05) (table 4). Between 1971 and 1985 two of the seven patients who were not treated with anticoagulants had a cerebral embolus and one had cerebral bleeding related to severe thrombopenia. Neurological signs were an early manifestation of endocarditis occurring before the start of treatment, in six of 11 cases between 1971 and 1980 and in the two recent cases with cerebral events.

PROGNOSTIC FACTORS
There was no significant difference in mortality (expressed as a percentage of cases) between men (12 of 30 (40%)) and women (nine of 16 (56%)), or between cases with mitral endocarditis (five of 11 (45%)), aortic endocarditis (eight of 21 (38%)), tri-

Table 4 *Correlation between neurological complications and anticoagulant treatment in cases of late prosthetic valve endocarditis occurring during two periods*

	Number of cases with cerebral events as a proportion of cases	
	1971–80	*1981–85*
Anticoagulants given	9/27	1/16
Adequate anticoagulation	3†/18*	1†/14
Inadequate anticoagulation	6‡/9*	0/2
Anticoagulants not given	2/2	1/5
Total	11/29	2/21

*p < 0·05.
†Probable embolus in two cases and probable haemorrhage in two cases.
‡Probable embolus in three cases and probable haemorrhage in three cases.

cuspid endocarditis (one of three (33%)), or multiple valve endocarditis (seven of 15 (47%)). The age of these who died and those who survived was similar. When heterograft valves were affected the death rate was 25% (two of eight cases). This was not significantly different from the death rate in endocarditis of mechanical valves (19 of 42 cases (45%)). The results of cross sectional echocardiography combined with pulsed Doppler could only be studied from 1981 to 1985. This technique provided evidence for the diagnosis of endocarditis—that is, vegetations (seven cases) or valve dysfunction (six cases) in 11 of the 19 cases studied. Two of the seven cases with vegetations died. Six of them had had valve replacement.

Several factors were associated with a less favourable outcome (tables 5 and 6). The predictive value (that is the number of deaths compared with the

Table 5   *Comparison of factors in the prognosis in late prosthetic valve endocarditis between two periods. Figures are numbers of deaths/numbers of cases*

	1971–80	1981–85	Significance
Cardiac failure with new regurgitant murmur	8/9	1/7	p = 0·01
Conduction abnormality	3/3	—	
Neurological event	10/11	2/2	NS
Persistent fever	6/9	3/11	NS
Streptococcal infection	3/13	1/10	NS
Non-streptococcal infection	14/16	3/11	p < 0·05
Total	17/29	4/21	p < 0·01

NS, not significant.

Table 6   *Comparison of the mortality in late prosthetic valve endocarditis between two periods, according to the treatment. Figures are numbers of deaths/number of cases (%)*

	1971–80	1981–85	p value
Antimicrobial agents alone	11/21 (52)	2/10 (20)	NS
Antimicrobial agents + operation	6/8 (75)	2/11 (18)	<0·05
Total	17/29 (59)	4/21 (19)	<0·01

NS, not significant.

Table 7   *Comparison of the mortality in late prosthetic valve endocarditis between two groups treated during two periods, according to the type of micro-organism and the treatment. Figures are numbers of deaths/number of cases*

	Antimicrobials alone	Antimicrobials and operation
Streptococcal endocarditis:		
1971–80	3/11	0/2
1981–85	0/5	1/5
Non-streptococcal endocarditis:		
1971–80	8/10	6/6*
1981–85	2/5	1/6*

*p = 0·015.

number of cases with the risk factor) of atrioventricular conduction abnormality, fever persisting for over 10 days despite adequate antibiotic treatment, and neurological complication was similar during both periods. Cardiac failure caused by valve dysfunction was indicative of poor prognosis in the first period only. An isolated new regurgitant murmur was not associated with a poor prognosis—two patients of the eight cases died. Neither was operated upon. The prognosis of cases of non-streptococcal endocarditis (14 deaths out of 16 cases) was significantly worse than the prognosis of cases of streptococcal endocarditis (three deaths out of 13 cases) between 1971 and 1980 (p < 0·001). However, from 1981 to 1985 the outcome of these two groups was not different; there were three deaths out of 11 cases of non-streptococcal endocarditis and one death out of 10 cases of streptococcal endocarditis.

The mortality associated with the type of organism and treatment during the two periods could not be compared because the numbers of cases were too small. The prognosis of surgically treated cases of non-streptococcal endocarditis seems to be better in the second period, however (table 7).

Discussion

This study indicates a considerable improvement in the prognosis of late prosthetic valve endocarditis between 1971–80 and 1981–85. The overall mortality was similar to that seen in a review of published series in 1982 in which the case-fatality rate for 193 cases was 46%.[2] Many factors may have contributed to this trend; some are related to the general improvement in medical care and surgical procedures and are thus difficult to analyse. Thus the differences between two successive periods must be interpreted with care. But an improvement in the treatment of late prosthetic valve endocarditis has been noted by others too.[4 9 10]

A comparison of clinical features in our study showed that the pattern of the disease has not changed significantly, except for a decrease in the frequency of neurological events in recent years. Neurological complications are one of the most important causes of death in prosthetic valve endocarditis[6 11] and they are usually associated with a high death rate.[8] A reduction in their occurrence may have been a major factor accounting for the improvement in prognosis between 1981 and 1985. This trend may be related to a change in the management of anticoagulants in recent years. The use of anticoagulants in late prosthetic valve endocarditis has been controversial.[8 11–14] Wilson *et al* emphasised that they should be temporarily discontinued only if a neurological event occurred.[15] In

our series anticoagulant treatment was continued in all patients to whom they had been given before the development of endocarditis. The position of patients who are not on anticoagulants when endocarditis is diagnosed is still being debated.[11] [12] The numbers of such patients have increased with the use of heterograft valves, which do not require long term anticoagulation.

Our study confirms that anticoagulation must be maintained in a narrow therapeutic range to decrease the frequency and the severity of neurological complications.[16] [17] We believe that intravenous heparin sodium is the best anticoagulant for patients with prosthetic valves. Stable anticoagulation cannot be achieved with warfarin, which may be affected by other drugs and infection.[18] The increased use of heparin sodium in our patients probably contributed to the decrease in neurological complications and thus to the improvement in prognosis during recent years. The only two neurological events that occurred between 1981 and 1985 were the first manifestation of endocarditis in both cases. We believe that heparin sodium should be used routinely when anticoagulants are indicated and as soon as the diagnosis of late prosthetic valve endocarditis is suspected.

Bacteriological factors may also have influenced the changing prognosis of late prosthetic valve endocarditis. Like others we found that streptococcal endocarditis was associated with a better outcome than other infections.[2] [15] In our study the predominance of streptococci and the less common occurrence of staphylococci (especially *Staphylococcus aureus*) may have reduced mortality in 1981–85; however, the prognosis of streptococcal endocarditis was not different in the two periods, whereas there was a pronounced improvement in the outcome of non-streptococcal endocarditis in recent years.

Advances in treatment in the past few years have improved the prognosis of patients with prosthetic valve endocarditis.[19] The effect of better medical management is difficult to assess. The principles of antimicrobial treatment remained the same—that is, a combined drug regimen of bactericidal agents with bacteriological tests[2] [15]—however, more potent antibiotics may have improved the prognosis of patients with non-streptococcal endocarditis.[20]

Differences in surgical treatment between the two periods are more obvious. An analysis of prognostic factors from 1971 to 1980[6] led us to formulate more precise indications for operation in recent years; these were based on the same criteria as those established by Karchmer *et al*.[8] The significant decrease in mortality of surgically treated cases between the two periods is probably another important factor in the improved prognosis in our series. Similar findings were reported by Mayer and Schoenbaum[2] when they reviewed five series.[7] [16] [21–23] We found that improved surgical management[24–26] was of particular benefit in those with non-streptococcal endocarditis (table 7).

Our study confirmed the validity of most of the criteria for operation established by Karchmer *et al*[8] and reviewed by others.[15] [27] Unlike others we did not find that aortic and mechanical valves were associated with a worse prognosis.[5] [9] [27] The presence of heterograft valves in the patients seen between 1981 and 1985, however, may have been instrumental in reducing the death rate. Cardiac failure due to valve dysfunction did not cause a higher death rate in recent years; all seven cases were treated by surgery. Embolic manifestations, infection with a fungal agent, and relapse have also been proposed as indications for operation,[8] [15] [27] but these cannot be evaluated in our study. The prognostic value of echocardiographic abnormalities must be confirmed by more extensive studies. Multiple factorial analysis of a greater number of cases may provide more precise indications for operation. Operation is an important factor in the improvement of prognosis of late non-streptococcal prosthetic valve endocarditis.

References

1 Geraci JE, Dale AJD, McGoon DC. Bacterial endocarditis and endarteritis following cardiac operations. *Wis Med J* 1963;62:302–15.

2 Mayer KH, Schoenbaum SC. Evaluation and management of prosthetic valve endocarditis. *Prog Cardiovasc Dis* 1982;25:43–54.

3 Watanakunakorn C. Prosthetic valve infective endocarditis. *Prog Cardiovasc Dis* 1979;22:181–92.

4 Richardson JV, Karp RB, Kirklin JW, Dismukes WE. Treatment of infective endocarditis. A 10 years comparative analysis. *Circulation* 1978;58:589–97.

5 Masur H, Johnson WD. Prosthetic valve endocarditis. *J Thorac Cardiovasc Surg* 1980;80:31–7.

6 Leport C, Vilde JL, Bricaire F, *et al*. Late prosthetic valve endocarditis: bacteriological findings and prognosis in 29 cases. *Eur Heart J* 1984;5:139–43.

7 Dismukes WE, Karchmer AW, Buckley MJ, Austen WG, Swartz MN. Prosthetic valve endocarditis. Analysis of 38 cases. *Circulation* 1973;48:365–77.

8 Karchmer AW, Dismukes WE, Buckley MJ, Austen WG. Late prosthetic valve endocarditis. Clinical features influencing therapy. *Am J Med* 1978;64: 199–202.

9 Rossiter SG, Stinson EB, Oyer PE, *et al*. Prosthetic valve endocarditis. Comparison of heterograft tissue valves and mechanical valves. *J Thorac Cardiovasc Surg* 1978;76:795–802.

10 Westaby S, Oakley C, Sapsford RN, Bentall HH. Sur-

gical treatment of infective endocarditis with special reference to prosthetic valve endocarditis. *Br Med J* 1983;**287**:320–3.

11 Carpenter JL, McAllister CK, and the US Army Collaborative Group. Anticoagulation in prosthetic valve endocarditis. *South Med J* 1983;**76**:1372–5.

12 Horstkotte D, Korfer R, Loogen F, Rosin H, Bircks W. Prosthetic valve endocarditis. Clinical findings and management. *Eur Heart J* 1984;**5**:117–22.

13 Wilson WR, Geraci JE, Danielson GK, *et al*. Anticoagulant therapy and central nervous system complications in patients with prosthetic valve endocarditis. *Circulation* 1978;**57**:1004–7.

14 Johnson WD. Prosthetic valve endocarditis. In: Kaye D, ed. *Infective endocarditis*. Baltimore: University Park Press, 1976:129–42.

15 Wilson WR, Danielson GK, Giuliani ER, Geraci JE. Prosthetic valve endocarditis. *Mayo Clin Proc* 1982;**57**:155–61.

16 Garvey GJ, Neu HC. Infective endocarditis: an evolving disease. *Medicine (Baltimore)* 1978;**57**:105–26.

17 Pruit IT, Rubin RH, Karchmer AW. Neurological complications of bacterial endocarditis. *Medicine (Baltimore)* 1978;**57**:329–43.

18 Qureshi GD, Reinders TP, Somori GJ, Evans HJ. Warfarin resistance with nafcillin therapy. *Ann Intern Med* 1984;**100**:527–9.

19 Ivert TSA, Dismukes WE, Cobbs CG, *et al*. Prosthetic

20 Karchmer AW, Archer GL, Dismukes WE. Rifampin treatment of prosthetic valve endocarditis due to *Staphylococcus epidermidis*. *Rev Infect Dis* 1983;**5**: 543–8.

21 Slaughter L, Morris JF, Starr A. Prosthetic valvular endocarditis. A 12 year review. *Circulation* 1973;**47**: 1319–26.

22 Wilson WR, Jaumin PM, Danielson GK, *et al*. Prosthetic valve endocarditis. *Ann Intern Med* 1975;**82**: 751–6.

23 Saffle JR, Gardner P, Schoenbaum SC, Wild W. Prosthetic valve endocarditis. The case for prompt valve replacement. *J Thorac Cardiovasc Surg* 1977; **73**:416–20.

24 Lau JKH, Robles A, Cherian A, Ross DN. Surgical treatment of prosthetic endocarditis. Aortic root replacement using a homograft. *J Thorac Cardiovasc Surg* 1984;**87**:712–6.

25 Donaldson RM, Ross DN. Homograft aortic root replacement for complicated prosthetic valve endocarditis. *Circulation* 1984;**70**:178–81.

26 Raychaudhury T, Cameron EWJ, Walbaum PR. Surgical management of prosthetic valve endocarditis. *J Thorac Cardiovasc Surg* 1983;**86**:112–4.

27 Baumgartner WA, Miller C, Reitz BA, *et al*. Surgical treatment of prosthetic valve endocarditis. *Ann Thorac Surg* 1983;**35**:87–104.

valve endocarditis. *Circulation* 1984;**69**:223–32.